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REVIEW

Asthma in pregnancy — Immunological changes and clinical management

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Summary

Asthma is one of the most common diseases complicating pregnancy and a risk factor for several maternal and fetal complications, posing a special challenge for physicians treating asthmatic pregnant women. Asthma influences the outcome of pregnancy and – vice versa – pregnancy affects asthma severity with bidirectional immunological interactions that are currently being examined. Supporting pregnancy-induced immunotolerance is the observation that attenuation of allergic responses can be detected in controlled asthmatic pregnant patients. However, uncontrolled asthmatic pregnant women show significant asthma-associated immune reactions, such as diminished pregnancy specific regulatory T cell proliferation, that may – besides other factors – influence fetal growth. Uncontrolled, symptomatic asthma may increase the risk of adverse perinatal outcomes; thus adequate regular anti-asthmatic treatment resulting in optimal asthma control represents a vital need during pregnancy. This review summarizes immunological changes characterizing pregnancy in asthmatic women together with the clinical implications of asthma management during pregnancy.

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Introduction

Asthma is one of the most common chronic diseases complicating pregnancy, affecting 3.7–8.4% of all pregnancies.¹ Pregnant women with asthma represent a special challenge for asthma specialists. Asthma influences the outcome of pregnancy and vice versa – pregnancy affects asthma severity, and the underlying immunological mechanisms of this interaction are currently being studied. Asthma represents a risk factor for several maternal and fetal complications, such as asthma exacerbations, use of oral corticosteroids, hospitalizations due to asthma attacks, preeclampsia, gestational hypertension, preterm delivery, cesarean delivery, low birth weight, intrauterine growth restriction, and fetal death.^{2–7} Thus, managing asthma during pregnancy requires careful decision making, optimal physician training, and frequent patient consultations with physicians treating these patients. Adequate management of asthma and maintenance of optimal asthma control during pregnancy decrease maternal and neonatal risks.^{8,9}

Immunological and clinical influence of asthma on pregnancy

Pregnancy is characterized by a physiological immunosuppression, an immunological tolerance that protects the fetus from maternal immune response against paternal antigens expressed by the fetus.¹⁰ Physiological pregnancy has been described as a Th2-dominated state, and current studies show that a trimester dependent, pregnancy-induced increase in regulatory T cell (Tregs) number has a key role in the maintenance of maternal tolerance to paternal antigens during pregnancy, exerting an inhibition on the activation of effector T lymphocytes and NK cells.¹¹ Diminished numbers of Tregs in pregnancy were associated with immunological rejection of the fetus as well as preeclampsia and low fetal birth weight.¹² Of note, Tregs exert inhibitory effects on natural killer lymphocytes responsible for protection against viruses¹³ that may contribute to increased susceptibility to viral infections (e.g. influenza) during pregnancy, as observed by H1N1 influenza in 2009.¹⁴

Asthma is traditionally also considered as allergic T helper cell 2 (Th2) type inflammation that leads to bronchial hyperresponsiveness, airway obstruction and – in some cases – tissue remodeling.¹⁵ Immunological changes in asthmatic women during pregnancy are not well elucidated. Previously we found signs of pregnancy-induced attenuation of allergic responses in asthmatic pregnant women. Activated pools within CD4 and CD8 T cells were larger, and the number of natural killer T (NKT) cells was increased both in non-pregnant asthmatic and in healthy pregnant subjects (compared with non-pregnant healthy controls), but in

(mostly well controlled) pregnant asthmatics no further lymphocyte activation was observed, suggesting that the immunosuppressive effect of uncomplicated pregnancy may blunt lymphocyte activation which characterizes asthma.¹⁶ In addition, as a sign of an enhanced T cell apoptosis, higher number of CD95⁺ T cells was detected in healthy pregnant than in healthy non-pregnant women, together with a positive correlation between CD95⁺ T cell counts and birth weights in healthy but not in asthmatic pregnancies.¹⁶

On the other hand, in another study enrolling mostly not well-controlled asthmatic pregnant women, a substantial number of peripheral interferon(IFN)- γ producing cells was detected, and a significant negative correlation was revealed between the number of IFN- γ positive T cells and birth weight of newborns, suggesting that fetal growth restriction (intra-uterine growth restriction – IUGR) can be related to active, asthma-associated maternal immune reactions.¹⁷ In addition, considering another inflammatory marker, heat shock protein(Hsp)-70, higher circulating levels were detected in asthmatic than in healthy pregnant women, and fetal birth weight was lower in pregnancies complicated with asthma, again suggesting – a relationship between asthmatic immune responses and altered fetal growth.¹⁸ In a recent study we found lower prevalence of peripheral Treg cells in asthmatic compared to healthy pregnant women.¹⁹ In healthy pregnancies the supposed relationship between strengthened maternal immunotolerance and the physiological growth of the fetus was reflected by a positive correlation between Treg prevalence and the birth weight of newborns. On the contrary, no correlation was detected between Treg prevalence and neonatal birth weight in the pregnancies of asthmatic women, either examining all pregnancies in asthmatic women or stratifying the analyses by female or male offspring. In addition, in asthmatic pregnant patients treated regularly with inhaled corticosteroids (ICS) a trend towards higher Treg cell prevalence was observed compared to those with inadequate adherence to ICS treatment.¹⁹

Immunological changes characterizing pregnancy in asthmatic women may contribute to the increased risk for maternal and fetal complications. In a database cohort of 13 100 pregnant asthmatics, a 35% increased risk of perinatal mortality was observed in the pregnancies of women with asthma.⁴ Another recent study⁸ of pregnant women with physician-diagnosed asthma evaluated their asthma control repeatedly during pregnancy based on symptom frequency and interference with daily activities and sleep and reported hospitalizations and unscheduled clinic visits for asthma exacerbations. According to their results, the incidence of preterm delivery is higher among patients with inadequate asthma symptom control during the first part of pregnancy compared with patients with adequate asthma control, and patients who are hospitalized for asthma during pregnancy have a higher incidence of preterm delivery compared with

asthmatic women without a history of hospitalization. Thus there may be a risk for preterm delivery posed by poorly controlled maternal asthma.⁸ According to a population-based cohort of 13 007 pregnancies in asthmatic women, mothers with severe and moderate asthma during pregnancy

have a higher risk of small for gestational age babies than those with mild asthma.²⁰ Finally, asthma also affects newborns' morphometry, as asthma severity was associated with an increased head circumference: birth weight ratio in a recent multicenter prospective observational cohort

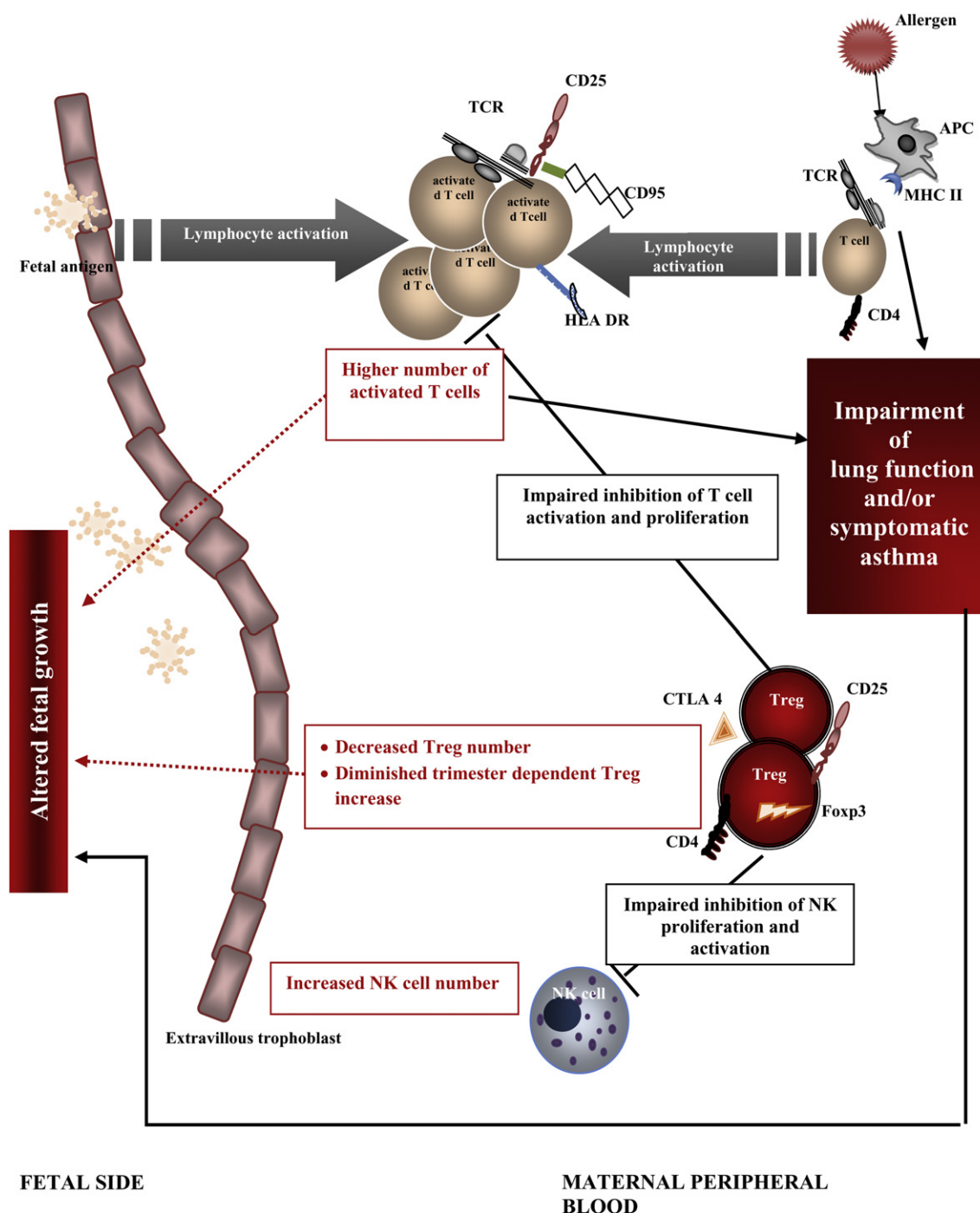


Figure 1 Immunological changes characterizing asthmatic pregnancy (red arrows) that may compromise physiological fetal growth. Absence of trimester dependent regulatory T cell elevation in asthmatic pregnancy leads to impaired inhibition of T lymphocyte and NK cell activation and proliferation. Elevated numbers of activated effector T lymphocytes and NK cells may cause immune mediated alteration of fetal growth and enhancement of allergic/asthmatic responses. (CD – cluster of differentiation; Foxp3 – fork head/winged-helix transcription factor box p3; L – ligand; TCR – T cell receptor; CTLA – cytotoxic T lymphocyte-associated antigen; APC – antigen presenting cell; MHC – major histocompatibility complex antigen HLA – human leukocyte antigen; Treg – regulatory T cell; NK – natural killer; → stimulation; ⊥ – inhibition).

study.²¹ Some immunological mechanisms characterizing asthmatic pregnancy and presumably leading to altered fetal growth are presented in Figure 1.

Effect of pregnancy on the course of asthma

Pregnancy may alter the natural course of asthma. Asthma improves during pregnancy in about one-third, remains the same in another one-third, and worsens in one-third of pregnant women. More severe asthma before pregnancy increases the risk of worsening during pregnancy, and there is a concordance between the courses of asthma during subsequent pregnancies.²² Asthma-specific quality of life in early pregnancy is related to subsequent asthma morbidity during pregnancy.²³

Severity of asthma symptoms during pregnancy may also be influenced by fetal gender. Worsened asthma symptoms²⁴ and higher incidence of IUGR²⁵ were observed in asthmatic pregnant women with female fetuses. Our latest results also demonstrated a higher risk for lack of asthma control and altered fetal growth in the pregnancies of asthmatic women carrying female fetuses.¹⁹ Obesity is associated with an increased risk of asthma exacerbations during pregnancy as well.³ Pregnancy-induced immunological tolerance may be altered in obese pregnant asthmatic women, as a lower prevalence of naive T cells was observed in obese compared to non-obese asthmatic pregnant patients.¹⁹ In addition, maternal obesity is associated with higher risk of non-pulmonary complications (e.g. preeclampsia, gestational diabetes, and gestational hypertension) in asthmatic pregnant patients.³ However, in spite of the above information, the immunological mechanisms causing alterations in the course of asthma, or serving as biomarkers for disease deterioration during pregnancy are mostly unknown.

Management of asthma during pregnancy

Diagnosis and monitoring

The diagnosis of asthma is usually known already before pregnancy. However, if first symptoms occur during

gestation, reduced forced expiratory volume in one second (FEV₁) or ratio of FEV₁ to forced vital capacity (FVC) and a 12% or greater improvement in FEV₁ after inhalation of rapid acting beta-agonist confirm the diagnosis of asthma. Testing bronchial hyperresponsiveness is contraindicated during pregnancy (because of the lack of safety data); thus women with a clinical picture of new-onset asthma without spirometric confirmation of the diagnosis should be treated for asthma during pregnancy. Skin prick tests are not recommended during pregnancy (risk of systemic reactions), but blood tests for specific IgE antibodies to suspected allergens may be evaluated.²⁶

Due to the bidirectional interactions between asthma and pregnancy and alterations of asthma severity during pregnancy, establishing optimal asthma management during gestation often represents a special challenge for the attending physician. Aim of the treatment is to achieve and maintain control of the disease. Fractionated concentration of nitric oxide present in exhaled breath (FE_{NO}) has been evaluated as a non-invasive tool for assessing airway inflammation in asthma,²⁷ and our recent study provided data supporting its applicability in asthmatic pregnant patients as well.²⁸

Pregnancy-induced hyperpnea causes somewhat higher arterial oxygen (pO₂ 100–105 mmHg) and lower arterial carbon-dioxide (PCO₂ 32–34 mmHg) partial pressures during normal pregnancy.^{29,30} Thus, even mild maternal hypoxaemia may represent respiratory compromise during pregnancy. Generally, maintenance of an arterial oxygen saturation of at least 95% measured by pulse oximetry is recommended to ensure sufficient oxygenation in both the mother and the fetus.²⁶

Treatment

Asthmatic pregnant patients should be educated regarding their disease and its treatment (Table 1), as recommended in current guidelines.^{7,26} Active (but not passive) smoking is associated with increased asthma symptoms and fetal growth abnormalities among pregnant women with asthma.³¹ Smoking cessation is necessary for asthmatic pregnant women, not only because of adverse effects of smoking on asthma and on pregnancy but also due to the known higher

Table 1 Main patient educational topics for asthmatic pregnant patients.

Main patient educational topics	Description
1. Information about the disease	Basic information about asthma and its relationship to pregnancy. Facts regarding maternal and fetal outcomes.
2. Use of inhaler devices	Demonstration of correct use of devices prescribed to the patient.
3. Adherence to treatment and importance of regular visits	Necessity of regular visits and appropriate controller medication during pregnancy complicated with asthma.
4. Environmental control measures to reduce exposure to allergens and irritants	Avoidance of known allergens and smoking.
5. Self-treatment action plan	Written schedule for maintenance therapy and doses of rescue medication for increased symptoms. Education about signs of asthma exacerbation and seeking urgent or emergency care. Education about controller medication increase or oral corticosteroid use for increased symptoms.

Table 2 Steps of asthma maintenance therapy during pregnancy (LTRA – leukotriene-receptor antagonist; LABA – long-acting beta-agonist).

Step	Preferred controller medication	Alternative controller medication
1	None	—
2	Low-dose inhaled corticosteroid	LTRA, cromolyn, theophylline
3	Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid + LABA or LTRA or theophylline
4	Medium-dose inhaled corticosteroid + LABA	Medium-dose inhaled corticosteroid + LTRA or theophylline
5	High-dose inhaled corticosteroid + LABA	—
6	High-dose inhaled corticosteroid + LABA + oral corticosteroid	—

risk for neonatal asthma in asthmatic pregnant women who smoke.³²

Most of the data on adverse effects of asthma medications in pregnancy are reassuring.²⁶ Observational studies of using inhaled beta-agonists and inhaled corticosteroids during pregnancy showed no increase in perinatal risks.^{33–36} The use of bronchodilators during pregnancy was associated with an increased risk of gastroschisis among infants in one study,³⁷ and higher risk of cardiac defects was observed in newborns of asthmatic mothers in another study.³⁸ However, asthma exacerbation itself during pregnancy may increase the risk of congenital malformations.³⁹

According to currently available safety data, albuterol is the reliever medication of choice during pregnancy. Budesonide is the preferred inhaled corticosteroid according to available data in human pregnancies.³⁵ Long-acting inhaled beta-agonists formoterol and salmeterol may be used as add-on therapy in pregnant patients if symptoms occur despite regularly used inhaled corticosteroid therapy. Leukotriene-receptor antagonists montelukast and zafirlukast seem also to be safe during gestation, but the available human data are limited.⁹ In one recent study enrolling 180 asthmatic pregnant women taking montelukast, no increase in the rate of major congenital malformations was observed.⁴⁰

Treatment of asthma during pregnancy must be aimed at controlling the disease (symptoms and lung function abnormalities as well). Asthmatic women with well-controlled asthma should continue taking their medications during pregnancy. Although guidelines recommend consideration of a step down in therapy in non-pregnant patients with well-controlled asthma for at least 3 months,^{7,9} controller treatment may be maintained in pregnant patients in order to reduce the risk of loss of asthma control during pregnancy. Therapy should be increased by one step in patients with asthma that is not well controlled (Table 2). A two-step increase, a course of oral corticosteroids, or both should be recommended for women with asthma that is very poorly controlled (Table 2).²⁶

Monthly asthma control assessment is recommended for women who require controller therapy during pregnancy. Optimal obstetrical care of not well-controlled asthmatic pregnant patients means more frequent ultrasonographic examinations (to monitor fetal growth, which can be affected by uncontrolled asthma) and assessment of fetal

well-being (nonstress testing from the 32nd gestational week). During labor and delivery the use of asthma medications should be continued. Women who are currently taking systemic corticosteroids or who have received several short courses of systemic corticosteroids during pregnancy are recommended to receive intravenous corticosteroids during labor and for 24 h after delivery.²⁶

In conclusion, asthma is one of the most common chronic diseases complicating pregnancy and influencing its outcome. Generally, although uncontrolled asthma may increase the risk of adverse perinatal outcomes, women with adequately-treated and well-controlled, disease during pregnancy do not appear to have a substantial increased risk of maternal or fetal complications. Frequent communication between obstetricians, asthma specialists, and general practitioners is vital in the treatment of asthma during pregnancy, as well as the development of an effective partnership between the patient and her health care professionals.

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Conflict of interest statement

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